Title: Audiological monitoring in Swiss childhood cancer patients

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Abbreviations:

AAA	American Academy of Audiology
AE	Audiological evaluation
ASHA	American Speech-Language-Hearing Association
BMT	Bone marrow transplantation
COG	Children's Oncology Group
CNS	Central nervous system
CI	Confidence interval
ENT	Ear-nose-throat
GPOH	German Society of Paediatric Oncology and Haematology
Gy	Gray
ICCC-3	International Classification of Childhood Cancer, Third edition
IQR	Interquartile range
OAE	Otoacoustic emissions
OR	Odds ratio
SCCR	Swiss Childhood Cancer Registry
SD	Standard deviation
SFOP	French Pediatric Oncology Society
SIOP	International Society of Paediatric Oncology
Std	Standardized
P	P-value

ABSTRACT

Background: Full audiological monitoring is the best strategy to detect hearing loss early and to provide timely intervention in the absence of a clinical method of otoprotection. Full monitoring requires audiological evaluation before, and then during and after ototoxic cancer treatment. In a worldwide context of monitoring protocols that vary substantially, we analyzed the audiological monitoring of childhood cancer patients over the last decade across treatment centers in Switzerland.

Procedure: We retrospectively searched for audiological evaluations in all nine Swiss Pediatric Oncology Centers. We analyzed proportions of patients who had audiological monitoring and described type and timing of monitoring. We determined predictors of audiological monitoring using multivariable logistic regression and described time trends.

Results: We included 185 patients from the Swiss Childhood Cancer Registry diagnosed 2005-2013 who had platinum chemotherapy and/or cranial radiation ≥30 Gray and who were alive at time of study. Less than half of children, 43%, had full audiological monitoring (before, during, and after treatment), while 72% were tested after cancer treatment. Non-study patients were less likely to have had monitoring in all phases of cancer treatment. Patients who received treatment with cisplatin or both platinum chemotherapy and cranial radiation were more likely to have had monitoring after treatment. Monitoring during and after treatment increased over the study period, but monitoring before treatment was insufficient in all time periods.

Conclusions: Our population-based study indicates that audiological monitoring is insufficient in Switzerland, particularly for non-study patients. Clinicians' must become more aware of the importance of full audiological monitoring.

INTRODUCTION

Platinum chemotherapy or/and cranial radiation can be toxic to the ear, a property called ototoxicity.[1-3] Platinum can cause sensorineural hearing loss due to toxic levels of reactive oxygen species in the cochlea that damage hair cells, the stria vascularis, and spiral ganglion cells.[1] Radiation ≥30 Gray (Gy) can cause sensorineural or conductive hearing loss due to direct damage to the external ear canal, the cochlea, the brainstem, or small vessels of the inner ear.[1] High-frequency hearing loss is most common and may progress unnoticed until communication problems become apparent.[1, 4] In children, moderate or even rather minimal hearing loss can impair speech development, cause learning problems, or reduce quality of life.[5-9] It is, therefore, crucial that hearing loss is detected early. Clinicians might have the option to discuss whether cancer treatment can be modified, they can counsel patients and parents, offer hearing aids and thus mitigate the downstream effects of hearing loss.

International guidelines[10-14] and clinical studies (Supplementary Table S1) recommend audiological monitoring because no clinical method of otoprotection yet exists.[15] Both the number of evaluations recommended and their timing vary substantially. However, all agree that full monitoring includes an initial audiological evaluation at baseline, before ototoxic treatment, to exclude any pre-existing hearing disorder; that evaluations should be repeated throughout the ototoxic treatment so that clinicians may modify cancer treatment; and that evaluation should continue after completion of cancer treatment to detect potential late-manifesting hearing loss. Patients receiving only cranial radiation should be evaluated both before and after radiation of ≥30 Gy. However, no study has yet investigated whether clinicians adhere to these recommendations, and whether patient characteristics or cancer treatment predict monitoring, or if participation in a clinical study plays a role in monitoring.

We characterized audiological monitoring in a national, registry-based sample of childhood cancer patients who received ototoxic cancer treatment. We analyzed predictors of

audiological monitoring and evaluated whether audiological monitoring improved over the last decade.

METHODS

Study population

The Swiss Childhood Cancer Registry (SCCR) is a nationwide, population-based registry that includes all children and adolescents residing in Switzerland who have been diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis prior to the age of 21.[16] Recent estimates indicate that the SCCR includes 91% of all patients diagnosed with cancer before the age of 16 in the years since 1985, and about 95% of those diagnosed since 1995.[17] The SCCR registers information on the diagnosis and treatment of the cancer and personal information. Tumors are classified according to the International Classification of Childhood Cancer, third edition (ICCC-3).[18] Ethics approval of analyses of SCCR data is granted by the Ethics Committee of the Canton of Bern to the SCCR (KEK-BE: 166/2014).

Inclusion criteria

We included all patients registered in the SCCR who were treated with ototoxic cancer treatment in the nine Swiss Pediatric Oncology Centers (Supplementary Fig. S1). We restricted the years of diagnosis to 2005-2013 because medical records from patients treated before 2005 are difficult to access due to Swiss data protection rules,[19] and the treatment and follow-up of patients diagnosed after 2013 was not finished when data collection ended in December 2015. We assumed that audiological monitoring may not have been the first priority in treating terminally ill children, and excluded the records of children who were not alive at the time of study; in any event, their medical records were often not available.[19]

We defined ototoxic cancer treatment as platinum chemotherapy or cranial radiation ≥30 Gy according to the literature.[11, 13, 14, 20, 21] To determine whether patients fulfilled the inclusion criteria, we obtained their personal and treatment-related information from the SCCR.

Chart review

We reviewed the medical records retrospectively. We collected audiological tests, the corresponding audiologists' reports, oncological discharge reports, and cancer treatment protocols in all nine Swiss Pediatric Oncology Centers and the corresponding ear-nose-throat departments.

Audiological monitoring

Through the end of 2015, we collected all audiological tests that were performed as part of care before, during, and after cancer treatment, and recorded the type and timing of evaluation. We categorized type of audiological test as pure tone audiometry, extended high frequency audiometry, free field audiometry, auditory brainstem response, otoacoustic emissions (OAE) testing, speech audiometry, or tympanometry. To assess the timing of audiological evaluation, we categorized tests as before, during, and after treatment. We divided the extent of audiological monitoring into two categories: i) full audiological monitoring included patients with at least one evaluation at all stages (before, during, and after cancer treatment); and ii) minimal audiological monitoring included patients with one or more evaluation that occurred only after treatment. Patients with cranial radiation were defined as having had full audiological monitoring if they received at least one evaluation pre- and post-treatment. We graded the most recent hearing test for each ear separately and for frequencies up to 8 kHz according to the SIOP Boston Ototoxicity Scale, which is more sensitive to detect hearing loss than other ototoxicity scales.[22, 23] We defined hearing loss as ≥grade 1 (>20 dB above 4kHz) according to the SIOP Boston Ototoxicity scale in the most affected ear, and graded severity from 0 to 4.[22]

Cancer treatment information

We collected detailed patient information on cancer treatment from the SCCR, or from the clinic archives when it was not available in the SCCR. We recorded the name and arm of the

clinical study, if applicable, the start and end dates of ototoxic cancer treatment, and dose of platinum chemotherapy or cranial radiation. We divided patients into three clinical study participation groups: patients officially registered in a clinical study; patients not registered in but treated according to a clinical study protocol (e.g., closed clinical study, study not open at the clinic); and patients who were treated but were neither registered in nor treated according to a study protocol. We classified patients into three ototoxic cancer treatment groups: cranial radiation ≥30 Gy, carboplatin, cisplatin, or both platinum chemotherapy and cranial radiation ≥30 Gy.

Statistical analysis

We first determined how many children had had at least one audiological evaluation overall, and at least one evaluation before, during, or after cancer treatment. To investigate whether audiological monitoring varies between subgroups, we stratified for age at cancer diagnosis, ototoxic cancer treatment, clinical study participation, and hearing status at the last audiological evaluation. We then characterized the types of audiological tests used before, during, and after treatment, overall and stratified for age at cancer diagnosis. In a third step, we determined the number of evaluations patients had among those who received any monitoring, and described the length of audiological follow-up after ototoxic cancer treatment. We only considered patients with ≥5 years between last ototoxic treatment and time of study to have similar chances to be monitored among patients. The fourth step assessed predictors of audiological monitoring by using logistic regression models. We first compared patients who had full audiological monitoring to all who did not have full audiological monitoring, and then compared patients who had minimal audiological monitoring to those without any audiological monitoring. We used gender, age at cancer diagnosis, ototoxic cancer treatment, and clinical study participation as independent variables. Finally, we assessed time trends in audiological monitoring. We compared proportions of

children who received audiological monitoring before, during, and after treatment between periods of cancer diagnosis, and tested for trends. To treat post-treatment differences with different lengths of follow-up equally, we considered only audiological evaluations within the first year after ototoxic treatment. We also used the Kaplan-Meier method to estimate cumulative incidence curves and calculated cumulative incidence for audiological monitoring 12 months after treatment stratified by period of diagnosis.

We used Stata (Version 13, Stata Corporation, Austin, Texas) for all analyses.

RESULTS

Characteristics of study population

Among 1,916 children diagnosed 2005-2013 with cancer, 306 had potentially ototoxic treatment and of these 210 were alive and eligible for the study. The medical records of 14 children were missing, and we excluded another 11 children who had been treated in Bellinzona, where both cancer care and follow-up are often shared with larger clinics and assessment of the complete medical records for a patient was not feasible. This resulted in 185 patients whose records were available for analysis (Supplementary Fig. S1, Table 1). The mean age (SD) of these patients was 7 (5) years at diagnosis and 11 (6) years at the most recent audiological evaluation. Table 1 gives details on clinical characteristics and cancer treatment of the study population. Fifty-six patients (30%) had a pathological result in the most recent audiological evaluation, among whom 25 patients (13%) had severity grade 1, while 21 patients (11%) had grade 2, 7 patients (4%) had grade 3, and 3 patients (2%) had grade 4.

Proportion tested, and type of audiological tests

Overall, 175 children (95%) treated with ototoxic cancer treatment had at least one evaluation, but only 78 children (42%) had full audiological monitoring in all phases of cancer treatment. Looking at each phase separately, 122 patients (66%) had at least one test before treatment, 125 (74%) were tested at least once during treatment, and 134 (72%) were tested one or more times after treatment (Table 2). Evaluation before treatment was more common in patients who were included in a clinical study or were treated according to a study protocol than in those whose treatment was not part of or conducted according to a study (73% and 64% respectively vs. 35%). Evaluation during treatment was less common in those younger than 5 years at diagnosis (60%), in those with carboplatin (61%), and in non-study patients (21%); and more common in patients older than 9 years at diagnosis (89%), in those

with cisplatin (81%) or with both platinum chemotherapy and cranial radiation ≥30 Gy (77%), or in those officially included in a clinical study (82%). Evaluation after treatment was less common in patients with cranial radiation ≥30 Gy (56%), in those with carboplatin (51%), or in non-study patients (24%), but more common in those with cisplatin (85%) or both platinum chemotherapy and cranial radiation ≥30 Gy (81%).

Pure tone audiometry, extended high frequency audiometry, and OAE testing were the most frequently used types of tests, independent of the time of treatment (Supplementary Table S2).

Frequency of audiological evaluations and follow-up period

Patients had in median one evaluation before, three during, or two after treatment (Table 3). During treatment, tests were more frequent in patients with both platinum chemotherapy and cranial radiation ≥30 Gy (P<0.001). After treatment, tests were done more often in patients older than 9 years at diagnosis (P=0.020), in study patients (P=0.036) and in those who have developed hearing loss (P<0.001). Patients who received ototoxic cancer treatment five or more years ago had a median audiological follow-up of 29 months. The longest follow-up had those who received cranial radiation of ≥30 Gy (median 56 months, P=0.013).

Predictors for full and minimal audiological monitoring

Full audiological monitoring differed with clinical study participation (Table 4). Full monitoring was less common in non-study patients (adjusted OR 0.1). Only one out of 17 children not treated according to a clinical study had full audiological monitoring. Minimal audiological monitoring differed with ototoxic cancer treatment and clinical study participation. It was more common in patients with cisplatin or both platinum chemotherapy and cranial radiation ≥30 Gy (adjusted OR 2.5, 1.5, respectively) and less common in non-study patients (adjusted OR 0.2). Only four out of 17 children not treated according to a clinical study had minimal audiological monitoring.

Time trends of audiological monitoring

Proportions of patients with audiological monitoring changed over the last decade (Fig. 1). In 2005-2006, 55% had at least one evaluation before treatment. That proportion increased to 79% in 2009-2010, but decreased back to baseline in 2013 (50%, P-trend=0.912). The proportion of patients with at least one evaluation during treatment increased from 68% in 2005-2006 to 88% in 2013 (P-trend=0.045), and the proportion with at least one evaluation 12 months after treatment increased from 42% in 2005-2006 to 60% in 2013 (P-trend=0.066). We found a nonsignificant trend towards an increasing cumulative incidence of auditory monitoring 12 months after treatment (P=0.059, Supplementary Fig. S2). Cumulative incidence of first audiological evaluation within 12 months after treatment was 45% (95% CI 31-62%) in those diagnosed 2005-2006, 52% (95% CI 38-68%) in those diagnosed 2007-2008, 60% (95% CI 45-74%) in those diagnosed 2009-2010, and 65% (95% CI 51-79%) in those diagnosed 2011-2012. Periods of diagnosis did not differ in age at diagnosis (P=0.666) or ototoxic cancer treatment (P=0.788).

DISCUSSION

This study of Swiss childhood cancer patients found that less than half of the children had full audiological monitoring that included an evaluation before, during, and after ototoxic cancer treatment. Seventy-two percent of study patients did receive at least one audiological evaluation after treatment, but non-study patients had significantly less audiological monitoring. Though monitoring during and after ototoxic treatment has become more frequent over the last decade, monitoring before treatment has been and remains insufficient.

Evaluations before treatment provide a crucial reference for assessing hearing changes, and are needed for ototoxicity grading scales.[10, 12, 24-26] They should therefore be as comprehensive as possible to have reference values for any evaluation conducted after ototoxic treatment. Yet in our study only 31 of 53 children (58%) at high risk to develop hearing loss from ototoxic therapy with platinum chemotherapy and cranial radiation had been monitored before treatment. Monitoring rates for baseline testing have been reported in other studies. Among seven oncologists and 16 audiologists in New Zealand who were interviewed to assess their knowledge of audiological monitoring of patients receiving potentially ototoxic treatment, all of the audiologists and six of the seven oncologists rated baseline evaluation as important.[27] Yet the clinicians had limited familiarity with guidelines, and their clinical practices varied, ranging from no routine monitoring to evaluations prior to each cycle of chemotherapy. A retrospective study in the U.S. found that hearing tests were performed at baseline in 71% of children with retinoblastoma treated under a Children's Hospital of Philadelphia protocol.[28] However, in a study of children under the age of 18 who were treated for solid tumors with cisplatin and/or carboplatin according to SFOP protocols between 1987 and 1997 at the institute Gustave-Roussy in France, a low proportion of patients, 34 of 120 (28%), received an audiometric evaluation prior to the first course of treatment.[29] These reports, as well as the

paucity of such studies in the literature, reinforce our observation that evaluation before treatment falls well short of the need for it.

Monitoring during treatment is specified by treatment protocols that have different monitoring schedules (Supplementary Table S1). For example, the Euramos protocol for osteosarcoma treatment used in 31 children in our study population suggested that only an evaluation before the 3rd and 4th cycle of cisplatin is needed. But, for 31 children treated according to HIT-2000, a protocol used to treat medulloblastoma, CNS PNET or ependymoma, monitoring was advised at each cycle of platinum chemotherapy. The protocol used to treat 10 children with medulloblastoma, ACNS0331, specified monitoring prior to every cisplatin cycle, which is in line with both American Academy of Audiology (AAA) and American Speech-Language-Hearing Association (ASHA) recommendations.[10, 12] Overall, 74% of our patients had at least one test during treatment. The percentage rose to 89% among patients who were older than 9 years, while 81% of those treated with cisplatin and 77% of those treated with both platinum chemotherapy and cranial radiation were tested at least once, as were 82% of those included in a clinical study.

After ototoxic treatment, the St. Jude Children´s research hospital protocol recommends yearly evaluation up to 10 years after cancer treatment (Supplementary Table S1).[30] However, the Children's Oncology Group Long-Term Follow-Up Guidelines recommend monitoring only if impairment is detected after treatment.[11] Variation across guidelines is by itself unlikely to explain why 28% of our patients received no evaluation after treatment. Participation in or treatment according to a clinical study improves monitoring. Thirteen of the 17 non-study patients received no post-treatment monitoring. Of these 17 non-study patients, 12 were diagnosed before the age of 5, 13 were diagnosed with retinoblastoma, and 12 were treated solely with carboplatin. In Switzerland, institutional treatment protocols do not specify standardized protocols for audiological monitoring for retinoblastoma patients,

and because carboplatin is less ototoxic clinicians may have performed fewer evaluations in this group.[1, 3] However, international guidelines do not exclude children treated only with carboplatin, and particularly for patients with retinoblastoma development of an additional sensory handicap is crucial.[31, 32] But conducting audiometry is challenging in this age group. Especially when young children are seriously ill, their cooperation and attention may be reduced, which can lead to hearing test results that have poor reliability, and to overall low testing rates.[22] In all cases, though, audiological monitoring for several years after cancer treatment is important as hearing loss may only appear many years later particularly for patients treated with cranial radiation.[3, 33]

Guidelines for audiological monitoring have changed over time. The 1994 ASHA guideline reported ototoxic effects only for platinum chemotherapy; audiological effects of cranial radiation were not well known at that time.[10, 34] Fifteen years later, the AAA guideline recommended annual monitoring for one to two years after cranial radiation.[12] Independent of monitoring schedules, evaluations themselves may be adjusted by, for example, focusing on the high frequencies that are critical in determining the onset of hearing loss.[24] In the current St. Jude Children's Hospital ototoxicity protocol, the number of evaluations depends on the platinum compound used or the dose of cranial radiation, but at least eleven hearing tests are recommended.[30] It is therefore no surprise that audiological monitoring during and after treatment has increased since 2005, though monitoring before treatment has not.

Our study was restricted to a retrospective review of charts from the clinics in which patients were treated for cancer. If any post-treatment evaluations were done in private practice our search would have missed them. To reduce this potential bias, we excluded patients treated in Bellinzona, a small clinic where identification of all medical documents was not feasible. With different guidelines recommending different numbers and timing of audiological evaluations, we simplified our definition of full audiological monitoring to

encompass only a single evaluation at each treatment stage. We may have overestimated the adherence to monitoring guidelines, because we had no information on the indication for every audiological evaluation. Testings may have been done for indications other than ototoxicity monitoring (e.g. repeated ear infections). Another reason for an overestimation could be that childhood cancer patients who developed hearing loss may have received audiological evaluation not only for detection, but also for follow-up of hearing loss. We also did not have detailed information on type of radiation. Patients irradiated with protons thus may have received a lower dose to the auditory system and be at lower risk of developing hearing loss than those who had photon radiation therapy. Hearing loss can also occur after radiation with doses <30 Gy, but we only included patients who received cranial radiation ≥30 Gy in the study population. Several studies suggest the cut-off of 30 Gy for ototoxicity.[11, 20, 21] We, therefore, expected clinicians to adhere to audiological monitoring guidelines only for those patients. Finally, our results cannot be extrapolated to children who died after cancer diagnosis.

Our study does have several strengths. Using unique data from medical records to investigate audiological monitoring, we were able to include patients with different childhood cancer diagnoses and different treatment protocols. Having exact dates of ototoxic exposure and audiological evaluations enabled us to analyze the timing of monitoring in detail. We also considered children diagnosed 2005-2013, which allowed us to evaluate changes over time.

Our results highlight how important it is to increase clinicians' compliance with audiological monitoring guidelines. We suggest clinicians comply with either recommendations of clinical studies or more general recommendations like the ASHA guideline, especially for non-study patients in the absence of a study protocol for audiological monitoring. We believe that compliance with audiological monitoring recommendations would increase if different clinical studies and guidelines harmonize numbers and timing of

audiological evaluations. The International Late Effects of Childhood Cancer Guideline Harmonization Group (www.ighg.org) is currently developing recommendations for ototoxicity monitoring after cancer treatment to unify existing recommendations and to provide optimum follow-up practices for audiological monitoring. This new guideline based on current literature, follow-up guidelines, and expert consensus will define who needs audiological monitoring, at what frequency, for how long, and what modality should be used.

In summary, our study indicates that audiological monitoring guidelines are insufficiently followed in Switzerland, particularly when patients are neither participants in a study nor treated according to a specific study protocol. We need to increase clinicians' knowledge of the importance of full audiological monitoring before, during, and after cancer treatment to increase compliance with international monitoring guidelines. Pediatric oncologists should be made aware of the need to send childhood cancer patients who will receive potentially ototoxic treatment to an audiologist for pretreatment monitoring. Standardized audiological monitoring that begins with a baseline evaluation is essential for the best possible audiological outcomes.

CONFLICTS OF INTEREST STATEMENT

The commercial funders of the Swiss Childhood Cancer Registry support the daily operation of the registry, but have not had nor will have any role in the design, conduct, or interpretation of any research project and related publications based upon the Swiss Childhood Cancer Registry.

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LEGENDS

Table 1 Characteristics of the study population.

Table 2 Proportion of patients with audiological monitoring before, during and after ototoxic cancer treatment.

Table 3 Frequency of audiological evaluations per patient (including only patients with at least one audiological evaluation).

Table 4 Predictors of audiological monitoring in childhood cancer patients.

Figure 1 Time trends in the proportion of childhood cancer patients with audiological monitoring.

*P-values derived from chi-square test for trend;
^We included only audiological evaluations within the first year after ototoxic cancer treatment.

Supplemenatry Table S1 Recommendations for audiological monitoring.

Supplemenatry Table S2 Type of audiological tests stratified by phase of ototoxic cancer treatment.

Supplemenatry Figure S1 Flow chart of study population.

[a]Including the following clinics: Kinderklinik Kantonsspital Aarau AG, Universitäts-Kinderspital Basel, Universitäts-Kinderklinik Inselspital Bern, Ospedale S. Giovanni Bellinzona, Hospital des Enfants Geneve, CHUV Lausanne, Kinderklinik Kantonsspital Luzern, Ostschweizer Kinderspital St. Gallen, Universitäts-Kinderspital Zürich
[b]Ototoxic cancer treatment defined as platinum chemotherapy or and cranial radiation ≥30 Gray.

Supplemenatry Figure S2 Cumulative incidence of first audiological evaluation after treatment.

P-value derived from log-rank test to test for equivalence of incidence curves.
We did not include patients diagnosed in 2013 as for some of those patients the period between the last ototoxic cancer treatment and the data collection was less than 12 months.

TABLE 1 Characteristics of the study population

	N=185 (%)
Gender	
Female	92 (50)
Male	93 (50)
Age at cancer diagnosis	
<5 year	73 (39)
5-9 years	41 (22)
10-16 years	71 (38)
Period of cancer diagnosis	
2005-2006	38 (21)
2007-2008	42 (23)
2009-2010	42 (23)
2011-2012	43 (23)
2013	20 (11)
Cancer diagnosis (ICCC-3)	
III: CNS tumor	72 (39)
IV: Neuroblastoma	16 (9)
V: Retinoblastoma	17 (9)
VI: Renal tumor	7 (4)
VII: Hepatic tumor	5 (3)
VIII: Bone tumor	35 (19)
IX: Soft tissue sarcoma	11 (6)
X: Germ cell tumor	22 (11)
Localisation	
Supratentorial	25 (14)
Infratentorial	42 (23)
Extracranial	25 (14)
Intraspinal	13 (7)
Others, not head	80 (43)
Type of clinical study[a]	
SIOP	64 (35)
GPOH & SFOP	75 (41)
COG	50 (27)
Clinical study participation	
Officially included in a clinical study	93 (50)
Treated according to a clinical study	75 (41)
Treated not according to a clinical study	17 (9)
Platinum chemotherapy	
Cisplatin	98 (53)
Mean (SD, range) dose in mg/m^2	*388 (141, 30-800)*
Carboplatin	92 (50)
Mean (SD, range) dose in mg/m^2	*3,072 (2,874, 400-18,661)*
Cranial radiation	69 (37)
Mean (SD, range) dose in Gy	*56 (8, 40-77)*
Brain surgery	65 (35)
Bone marrow transplantation	
No	171 (81)
Yes	14 (11)

Abbreviations: ICCC-3, International Classification of Childhood Cancer, Third edition; Gy, Gray; SIOP, International Society of Paediatric Oncology; COG, Children`s Oncology Group;

GPOH, German Society of Paediatric Oncology and Haematology; SFOP, French Pediatric Oncology Society; SD, standard deviation.
[a]Categories are not exclusive of each other: e.g., Euramos is included in COG and GPOH & SFOP.

TABLE 2 Proportion of patients with audiological monitoring before, during and after ototoxic cancer treatment

	Before treatment (n=185)			During treatment[a] (n=169)			After treatment (n=185)		
	No AE n (%)	≥1 AE n (%)	P	No AE n (%)	≥1 AE n (%)	P	No AE n (%)	≥1 AE n (%)	P
Overall	63 (34)	122 (66)		44 (26)	125 (74)		51 (28)	134 (72)	
Age at cancer diagnosis			0.143			0.001			0.102
<5 year (n=73)	29 (40)	44 (60)		28 (40)	42 (60)		26 (36)	47 (64)	
5-9 years (n=41)	16 (39)	25 (61)		9 (25)	27 (75)		11 (27)	30 (73)	
10-16 years (n=71)	18 (25)	53 (75)		7 (11)	56 (89)		14 (20)	57 (80)	
Ototoxic cancer treatment			0.068			0.050			<0.001
Cranial radiation ≥30 Gy (n=16)	5 (31)	11 (69)		-[a]	-[a]		7 (44)	9 (56)	
Carboplatin (n=49)	21 (43)	28 (57)		19 (39)	30 (61)		24 (49)	25 (51)	
Cisplatin (n=67)[b]	15 (22)	52 (77)		13 (19)	54 (81)		10 (15)	57 (85)	
Platinum and cranial radiation ≥30 Gy (n=53)	22 (42)	31 (58)		12 (23)	41 (77)		10 (19)	43 (81)	
Clinical study participation			0.009			<0.001			<0.001
Officially included in a clinical study (n=93)	25 (27)	68 (73)		15 (18)	70 (82)		23 (25)	70 (75)	
Treated according to a clinical study (n=75)	27 (36)	48 (64)		18 (26)	52 (74)		15 (20)	60 (80)	
Treated not according to a clinical study (n=17)	11 (65)	6 (35)		11 (79)	3 (21)		13 (76)	4 (24)	
Hearing loss at most recent audiological testing[c]			0.622			0.108			0.402
No (n=115)	35 (30)	80 (70)		26 (25)	80 (75)		27 (23)	88 (77)	
Yes (n=56)	15 (27)	41 (73)		7 (13)	45 (87)		10 (18)	46 (82)	

Abbreviation: AE, audiological evaluation, P, P-value.

[a]Only 169 patients, those treated with platinum, could have had audiological monitoring during treatment because monitoring is not conducted during treatment with cranial radiation.

[b]Includes 7 patients who received both cisplatin and carboplatin.

[c]Hearing outcome was not available for 14 patients.

TABLE 3 Frequency of audiological evaluations per patient (including only patients with at least one audiological evaluation)

	Before treatment		During treatment		After treatment			Audiological follow-up period in months[d]	
	Median (range)	P[a]	Median (range)	P[a]	Median (range)	Std. Median[b]	P[c]	Median (range)	P[a]
Overall	1 (1-3)		3 (1-17)		2 (1-13)	0.33		29 (1-112)	
Age at cancer diagnosis		0.792		0.054			0.020		0.553
<5 year (n=73)	1 (1-3)		2 (1-17)		2 (1-13)	0.28		41 (1-108)	
5-9 years (n=41)	1 (1-2)		4 (1-16)		2 (1-7)	0.33		25 (1-86)	
10-16 years (n=71)	1 (1-2)		3 (1-11)		2 (1-11)	0.42		28 (2-112)	
Ototoxic cancer treatment		0.295		<0.001			0.366		0.013
Cranial radiation ≥30 Gy (n=16)	1 (1-1)		-[f]		2 (1-11)	0.44		56 (30-64)	
Carboplatin (n=49)	1 (1-2)		2 (1-17)		2 (1-4)	0.28		17 (1-108)	
Cisplatin (n=67)[e]	1 (1-3)		3 (1-6)		2 (1-13)	0.33		34 (1-112)	
Platinum and cranial radiation ≥30 Gy (n=53)	1 (1-2)		4 (1-9)		2 (1-11)	0.40		29 (2-86)	
Clinical study participation		0.603		0.420			0.036		0.834
Officially included in a clinical study (n=93)	1 (1-3)		3 (1-17)		2 (1-13)	0.29		29 (1-112)	
Treated according to a clinical study (n=75)	1 (1-2)		3 (1-9)		2 (1-11)	0.40		30 (1-86)	
Treated not according to a clinical study (n=17)	1 (1-2)		1 (1-2)		1 (1-2)	0.20		8 (2-108)	
Hearing loss at most recent audiological testing		0.627		0.062			<0.001		0.281
No (n=115)	1 (1-2)		3 (1-17)		2 (1-7)	0.29		27 (1-108)	
Yes (n=56)	1 (1-3)		3 (1-9)		4 (1-13)	0.47		39 (4-112)	

Abbreviations: Std, Standardized; P, P-value.

[a]P-value derived from equality-of-medians test.

[b]Median is standardized for time between last ototoxic treatment and time of data collection. It shows the median number of audiological evaluations per year of follow-up.

[c]P-value derived from standardized median using equality-of-medians test.

[d]Includes only patients with ≥5 years between last ototoxic treatment and time of study.

[e]Includes 7 patients who received both cisplatin and carboplatin.

[f]Only those treated with platinum, could have had audiological monitoring during treatment because monitoring is not conducted during treatment

with cranial radiation.

TABLE 4 Predictors of audiological monitoring in childhood cancer patients

	Full audiological monitoring (≥1 audiological evaluation before, during, and after treatment) (n=78)				Minimal audiological monitoring (≥1 audiological evaluation after treatment) (n=134)			
	n (%[a])	Crude OR (95% CI)	Adjusted OR (95% CI)	P[b]	n (%[c])	Crude OR (95% CI)	Adjusted OR (95% CI)	P[b]
Gender				0.404				0.928
Female (n=92)	38 (41)	1.0	1.0		63 (68)	1.0	1.0	
Male (n=93)	39 (42)	1.0 (0.6-1.8)	0.8 (0.4-1.4)		71 (76)	1.5 (0.8-2.8)	1.0 (0.5-2.2)	
Age at cancer diagnosis				0.052				0.824
<5 years (n=73)	24 (33)	1.0	1.0		47 (64)	1.0	1.0	
5-9 years (n=41)	13 (32)	0.9 (0.4-2.2)	0.7 (0.3-1.8)		30 (73)	1.5 (0.7-3.5)	1.0 (0.4-2.5)	
10-16 years (n=71)	40 (56)	2.6 (1.3-5.2)	1.9 (0.9-4.1)		57 (80)	2.3 (1.1-4.8)	1.3 (0.5-3.2)	
Ototoxic cancer treatment				0.495				0.031
Cranial radiation ≥30 Gy (n=16)	7 (44)	1.0	1.0		9 (56)	1.0	1.0	
Carboplatin (n=49)	12 (24)	0.4 (0.1-1.4)	0.6 (0.2-2.1)		25 (51)	0.8 (0.3-2.5)	0.9 (0.3-3.2)	
Cisplatin (n=67)[d]	37 (55)	1.6 (0.5-4.8)	1.1 (0.3-3.7)		57 (85)	4.4 (1.3-14.6)	2.5 (0.7-9.1)	
Platinum and cranial radiation ≥30 Gy (n=53)	21 (40)	0.8 (0.3-2.6)	0.7 (0.2-2.5)		43 (81)	3.3 (1.0-11.1)	1.5 (0.7-3.3)	
Clinical study participation				0.006				0.010
Officially included in clinical study (n=93)	48 (52)	1.0	1.0		70 (75)	1.0	1.0	
Treated according to clinical study (n=75)	28 (37)	0.6 (0.3-1.0)	0.6 (0.3-1.2)		60 (80)	1.3 (0.6-2.7)	1.5 (0.7-3.3)	
Treated not according to a clinical study (n=17)	1 (6)	0.1 (0.1-0.5)	0.1 (0.0-0.6)		4 (24)	0.1 (0.1-0.3)	0.2 (0.1-0.8)	

Abbreviation: P, p-value; OR, odds ratio; CI, confidence interval.

[a]Proportions of children with full audiological monitoring of the total number of children in the respective category.

[b]P-value from multivariable regression using likelihood ratio test.

[c]Proportions of children with minimal audiological monitoring of the total number of children in the respective category.

[d]Includes 7 patients who received both cisplatin and carboplatin.

Supplemental

Supplementary TABLE S1 Recommendations for audiological monitoring

	Before treatment	During treatment	After treatment	Minimal number of evaluations in total	Grading scale	Type of audiological test
Clinical study protocol[a]						
ACNS0331 for Medulloblastoma	Yes	Prior to every cycle with cisplatin	Within 6 weeks of completion of chemotherapy, after 1 year, after 3 years, annually after 3 years, obtain at 5 years only if clinically indicated	6	CTCAE	Audiometry (not further specified)
HIT-2000 for Medulloblastoma/ CNS PNET/ Ependymoma	Yes	With each cycle of cis- or carboplatin, or radiotherapy (not specified whether before or after)	Once per year for the first two years; following years, individually	4	CTCAE	Tone audiometry
Euramos-1 for osteosarcoma	Yes	Prior 3rd and 4th AP cycle; after last cycle of chemotherapy	Within 4 weeks after chemotherapy. If no impairment found it is possible to stop, but audiological monitoring is recommended until 10 years after end of therapy.	5	CTCAE	Audiometry (not further specified)
Ototoxicity monitoring protocol						
ASHA 1994	Yes	Prior to every cycle of platinum chemotherapy	As soon as possible after treatment, 3 and 6 months after platinum chemotherapy	5	Not specified	Pure tone audiometry including high frequencies, otoscopy, tympanometry, speech audiometry
AAA 2009	Yes	Prior to each cycle of platinum chemotherapy	Few months after platinum chemotherapy Cranial radiation: annually 1-2 years	3	CTCAE, Brock´s hearing loss grades	Baseline testing with all tests needed in subsequent evaluations: pure tone audiometry including high frequencies, tympanometry, speech audiometry, OAE testing

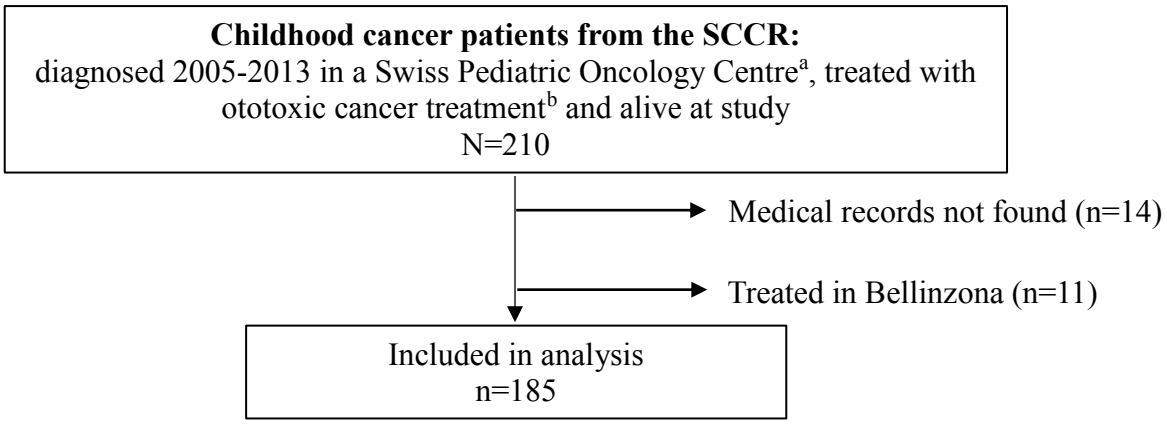
	Before treatment	During treatment	After treatment	Minimal number of evaluations in total	Grading scale	Type of audiological test
St. Jude Children´s research hospital ototoxicity protocol 2013	Yes	Cisplatin: prior to every cycle Carboplatin: prior to every 2-4 cycles	Platinum: at 3, 6, 9 and 12 months after treatment Cranial radiation: Low risk: annually for 5 years High risk[b]: every 6 months for 5 years Follow both groups annually for 5 additional years.	Platinum: 11 Cranial radiation: Low risk: 11 High risk: 16	Not specified	Baseline testing: Ototoscopy, tympanometry, pure tone audiometry including high frequencies, DPOAE testing, click and tone burst ABR/ASSR as indicated
Long-term follow-up guideline						
Children's Oncology Group 2013	NA	NA	History for hearing difficulties, tinnitus, otoscopic exam yearly. Platinum: Baseline at entry into follow-up. If impairment is detected, test at least yearly. Cranial radiation ≥30 Gray: Yearly for 5 years after treatment (by patients < 10 years continue yearly until age 10), then every 5 years. If impairment is detected, test at least yearly. If inconclusive or unevaluable, consider OAE.	NA as only follow-up is addressed	Not specified	Pure tone air and bone conduction, speech audiometry, and tympanometry for both ears. Frequency-specific auditory brainstem response can be performed if result is inconclusive.
Dutch Childhood Oncology Group 2010	NA	NA	Cisplatin: every 5 years Carboplatin: initial screen 5 years after treatment, if no abnormalities detected, no repeat testing is required Cranial radiation ≥30 Gray: initial screen 5 years afterwards, if no Abnormalities detected, no repeat testing required	NA as only follow-up is addressed	Not specified	Tone audiometry up to 12.5kHz and tympanometry

	Before treatment	During treatment	After treatment	Minimal number of evaluations in total	Grading scale	Type of audiological test
United Kingdom Children`s Cancer Study Group Late Effects Group 2011	NA	NA	After completion of treatment	NA as only follow-up is addressed	Not specified	Pure tone audiogram. In infants: behavioral audiometry, otoacoustic emissions, or auditory brainstem responses.

Abbreviations: AAA, American Academy of Audiology; ASHA, American Speech-Language-Hearing Association; AP-cycle, Doxorubicin-Cisplatin cycle; ASCT, autologous stem cell transplantation; NA, not applicable; CNS, central nervous system; CTCAE, Common Terminology Criteria of Adverse Events; DPOAE, distortion product otoacoustic emission; ABR, auditory brainstem response; ASSR, auditory steady-state response.

[a]We described the recommendations of the three most frequently used clinical study protocols in the study population.

[b] Cochlear exposure >35 Gray.



Supplementary Figure S1 Flow chart of study population.
[a]Including the following clinics: Kinderklinik Kantonsspital Aarau AG, Universitäts-Kinderspital Basel, Universitäts-Kinderklinik Inselspital Bern, Ospedale S. Giovanni Bellinzona, Hospital des Enfants Geneve, CHUV Lausanne, Kinderklinik Kantonsspital Luzern, Ostschweizer Kinderspital St. Gallen, Universitäts-Kinderspital Zürich
[b]Ototoxic cancer treatment defined as platinum chemotherapy or and cranial radiation ≥30 Gray.

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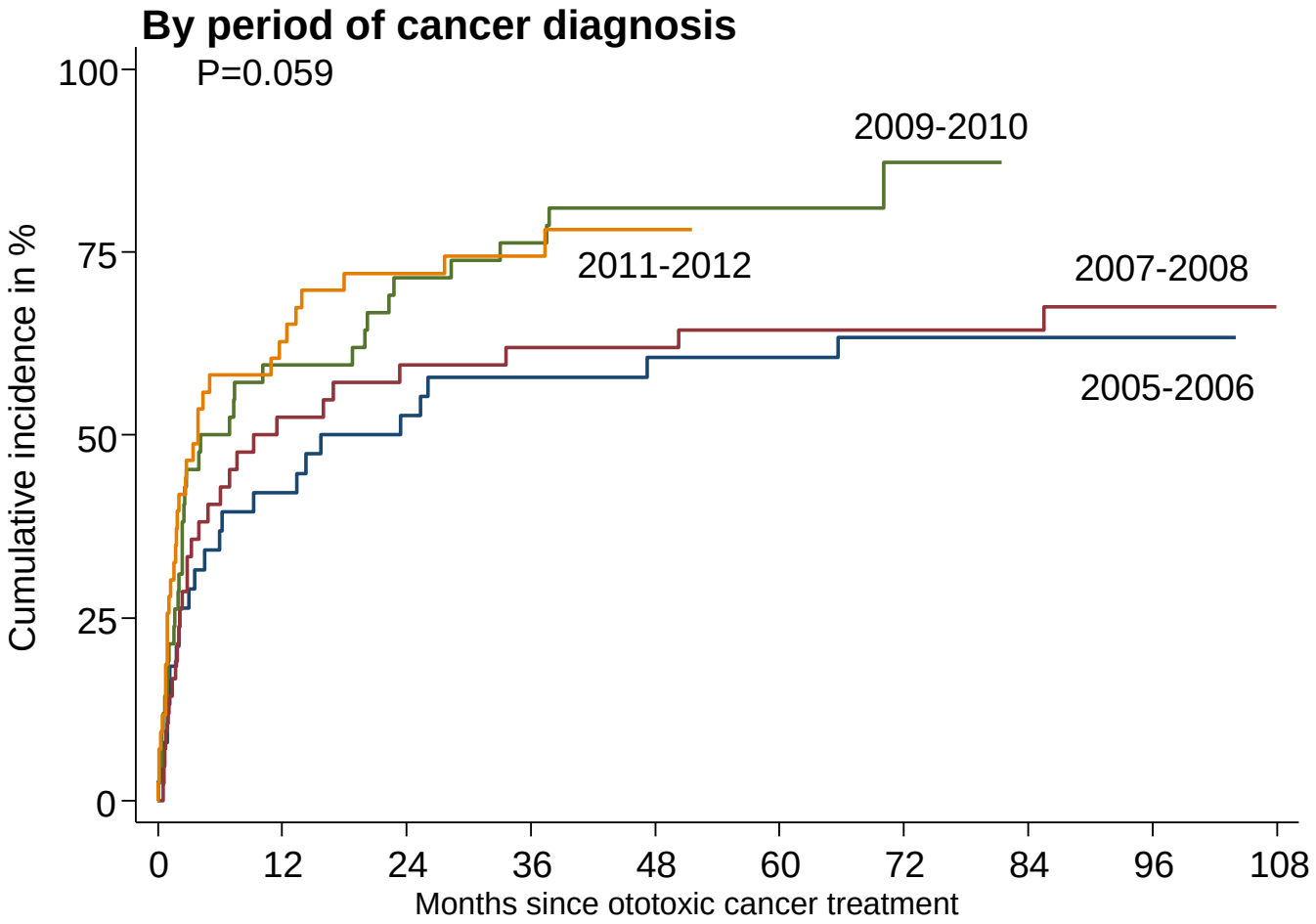
Supplementary TABLE S2 Type of audiological test, stratified by phase of ototoxic cancer treatment and age at diagnosis

Type of audiological test per patient	Before treatment		During treatment		After treatment	
Overall (n=185)	n (%)	max number of tests per patient	n (%)	max number of tests per patient	n (%)	max number of tests per patient
Pure tone audiometry	62 (33)	2	67 (36)	16	83 (45)	11
Extended high frequency audiometry	32 (17)	2	44 (24)	11	43 (24)	9
Free field audiometry	18 (9)	3	22 (12)	15	23 (12)	11
Auditory brainstem response	8 (4)	1	5 (3)	2	7 (4)	2
OAE testing	31 (17)	2	37 (20)	15	33 (18)	3
Speech audiometry	0 (0)	0	2 (1)	2	12 (6)	5
Tympanometry	10 (5)	1	18 (10)	4	28 (15)	5

Abbreviation: OAE, otoacoustic emissions



Supplementary Figure S2 Cumulative incidence of first audiological evaluation after treatment.
P-value derived from log-rank test to test for equivalence of incidence curves.
We did not include patients diagnosed in 2013 as for some of those patients the period between the last ototoxic cancer treatment and the data collection was less than 12 months.